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Medical Marijuana: Evaluating the Quality and Quantity of Evidence Available

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LEARNING OBJECTIVES

Upon completion of this module, the subscriber will be able to:

1. Identify the two major cannabinoids found in cannabis that are responsible for its effects on the human body.
2. List the synthetic formulations of cannabis that have been approved in the United States.
3. Given a pyramid of evidence, identify which type of study represents the best quality of evidence.
4. Identify which clinical indications have high-quality data supporting the effectiveness of medical marijuana.
5. List potential adverse effects and safety issues associated with the use of medical marijuana.

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Medical Marijuana: Evaluating the Quality and Quantity of Evidence Available

What is Marijuana/Cannabis

Cannabis is a naturally growing, flowering plant. There are three species: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*, of which *Cannabis sativa* is the most widespread.[1] Cannabis has been cultivated and farmed for many years for its hemp fiber, hemp oils, and medicinal properties. Cannabis originated from the Himalaya region and was imported to North America for use in rope, clothing, and paper.

Cannabis plants produce compounds called cannabinoids, which are responsible for the mind-altering effects (i.e. "high") that people experience after ingesting marijuana.[1] Of the approximately 400 chemical compounds present in cannabis plants; it is thought that there are at least 80 different cannabinoids present. Delta-9-tetrahydrocannabinol (THC) is the main psychoactive cannabinoid found in cannabis. Cannabidiol (CBD) is also thought to play a role in many disease states for which medical marijuana is used. Although it does not seem to be as psychoactive as THC, it is thought to work in other ways to improve disease states for which medical marijuana is used.

Cannabis can be consumed in many different ways. Marijuana refers to the dried leaves of the *Cannabis sativa* plant, which are used for medicinal (or recreational) purposes. Marijuana can be smoked from pipes, wrapped in paper like cigarettes (known as "joints") or wrapped in tobacco leaves (known as "blunts"). Other types of cannabis products are the resin (known as hashish) and the oil (known as hash oil). Marijuana usually contains up to 5% THC, whereas the resin can contain up to 20% and the oil up to 60%.[2] Cannabis can also come in several oral forms including tablets, extracts, and food preparations (i.e., candy or brownies). **Table 1** contains definitions of some of the terms that will be commonly used in this module.

History of Medical Marijuana

Although the use of marijuana for medicinal purposes has received much focus and attention recently, it has actually been used for many years. **Table 2** contains a timeline that

Table 1. Definitions[3]

Cannabinoid	A synthetic (i.e., man-made) cannabis compound. Includes: dronabinol, nabilone, and nabiximols.
Cannabidiol (CBD)	Another one of the major medicinal compounds found in cannabis that has little psychoactive properties.
Endocannabinoids	Naturally occurring cannabinoids inside the body that act at various cannabinoid receptors.
Marijuana	Dried leaves of the *Cannabis sativa* plant that are used for recreational or therapeutic properties.
THC	Delta-9 tetrahydrocannabinol. The main psychoactive component of cannabis.

outlines some of the regulatory history of marijuana.[3] Although it was introduced "officially" to the medical community in Europe in the early 1800s, it is likely that it was used much earlier than that. Some documentation indicates that marijuana was used for medicinal purposes as early as 2700 B.C.[4] In the United States (US), it was introduced into the US Pharmacopeia in 1850, where it was used until the mid 1930s. In 1937, it was criminalized in the US despite the American Medical Association (AMA) recommending against this.[5]

Formulations: Synthetic and Natural

There are two different kinds of cannabis products – the synthetic (i.e., non-natural or manufactured) cannabis-derived products that are approved in the US and other countries, and then there is the physical plant product, which we know as "medical cannabis". **Table 3** shows the synthetic cannabis-derived products approved in the US and other countries.

Dronabinol and nabilone are both oral products that were approved in 1985 for chemotherapy-induced nausea and vomiting (CINV) in patients who are not responding to other anti-nausea/vomiting agents.[6] In 1992, dronabinol (Marinol) received an indication for anorexia associated with weight loss in patients with acquired immune deficiency syndrome (AIDS).[6] Dronabinol was initially a schedule II substance, but was reclassified as a schedule III. Nabilone (Cesamet) is a cannabinoid that structurally looks a lot like THC. Nabilone is more potent than dronbabinol, which is why it remains a schedule II drug.[7] Dronabinol contains a synthetic version of THC. Nabilone is a synthetic substance that is structurally similar to THC. Nabixomols (Sativex) is a cannabis liquid extract that is available as an oromucosal spray.[8] It is not approved in the US but it is approved in Canada and in some European countries.

The plant version of marijuana is what is known as "medical marijuana" and it is classified federally as a schedule I substance. Most of the plants used medicinally come from *Cannabis sativa* or *Cannabis indica* species. Most of

Table 2. History of Medical Marijuana[3]

- Medical marijuana was introduced to the medical community in Europe in 1839
- Admitted to US Pharmacopoeia in 1850
- Used therapeutically in the US until mid-1930s
- 1937: Law prohibiting use passed by Congress (against the advice of the AMA)
- Removed from US Pharmacopoeia in 1942
- Approximately 40-50% of the US population has used marijuana in their lifetime

Table 3. Formulations[6,7,8]

Compound	Approved in US?	Indications	Formulations
Dronabinol (Marinol) Schedule III	Yes	• Second-line treatment of CINV • Anorexia/weight loss in patients with AIDS	Oral capsules
Nabilone (Cesamet) Schedule II	Yes	• Second-line treatment of CINV	Oral capsules
Nabiximols (Sativex)	No	• Second-line treatment of spasticity in adults with MS • Neuropathic pain in patients with MS • Intractable cancer pain	Cannabis-derived liquid extract available as an oromucosal spray

CINV – Chemotherapy induced nausea and vomiting
AIDS – Acquired Immune Deficiency Syndrome
MS – Multiple Sclerosis

the psychoactive effects of marijuana are believed to be due to the THC. Due to the uncontrolled production of medical cannabis, there can be very different concentrations of each of the endocannabinoid compounds (i.e., THC and CBD). Thus, it becomes a little more difficult to predict the type of response each plant can produce.[3]

How It Works: Pharmacology

Marijuana targets a number of different receptors throughout the body, but primarily affects CB1 and CB2 receptors. The areas where CB1 and CB2 receptors are found in high concentrations are listed in **Table 4**. A lot of what affects central nervous system (CNS) activity (psychoactive effects) is mediated through CB1 receptors, including: motor activity, coordination memory/thinking, and appetite (i.e., getting the "munchies").[3] CB2 receptors are found in immune cells and also in the brain. Of note, CB2 receptors are absent in the brain stem, which is why marijuana does not cause respiratory depression like opioids.[3]

Based on where it works in the human body and the receptors that it acts on, marijuana produces many different symptoms including: euphoria, psychosis, and decreased memory/ability to think. Marijuana may also produce some symptoms that may be considered "desirable" by patients with certain disease states – for example, it may increase appetite, which may be helpful for patients with decreased appetite due to cancer, or HIV/AIDS. It also has anti-emetic properties, which may be helpful in patients taking certain cancer regimens that induce nausea. It has also been shown to have pain-relieving effects and to help with muscle spasms, which has justified its use in medical conditions such as multiple sclerosis. A more detailed summary of the role of marijuana for these and other disease states is included later on in this module.[3]

There are as many as 80 different compounds present in marijuana and they each affect CB1 and CB2 receptors to varying degrees. Although the exact mechanism of action of medical marijuana has not been fully determined, its role in many disease states is thought to be primarily the result of the action of two compounds: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC produces many of the psychoactive effects of marijuana. Ingestion of THC leads to the following symptoms: increased heart rate, euphoria, decreased alertness, and decreased motor stability/coordination.[3]

CBD is another compound present in cannabis. A number of studies have shown that the presence of this compound actually decreases the psychotropic activity of THC. CBD may also have some anti-inflammatory components, or immunogenic (immune stimulating) properties.[3] Some dispensaries are creating new formulations that essentially involves hybridizing plants to contain both of these products (THC and CBD). This way, the user can get some of the therapeutic benefits without as much of the psychotropic effects.

Pharmacokinetic Properties

There have been a few small studies that have evaluated the pharmacokinetics of smoked marijuana. In general, marijuana is a highly lipophilic drug, meaning that it tends to stay in fat cells. Once ingested, the active components of marijuana stays in the body for a long time; the half-life of THC is around 30 hours and that of CBD around 9 hours. The half-life is the time it takes for half of the drug to be eliminated.

The amount of THC that is actually absorbed into the body once it is smoked is highly variable. When burned, about 50% of the THC is converted to smoke and the rest is lost by burning or is not inhaled. Of the remaining 50%, some is exhaled, and some metabolized in the lungs. Therefore, the amount that is actually absorbed into the body can vary widely from person to person and is dependent on the way it is inhaled.[3] Thus, dosing is less precise than what we are used to with approved medications. This also makes it difficult to modify the dose with smoked formulations. Effects are seen within minutes of ingestion with the inhalational route.

Table 4. How Marijuana Works[3]

CB1 receptors
- Basal ganglia (motor activity)
- Cerebellum (motor coordination)
- Hippocampus (short-term memory)
- Neocortex (thinking)
- Hypothalamus and limbic cortex (appetite and sedation)
- Periaqueductal gray dorsal horn (pain modulator)
- Immune cells

CB2 receptors
- Immune cells
- Brain (Alzheimer's Disease)

Similar issues with variable absorption are found with the oral formulations of cannabis. In addition, when ingested orally, there is often a delay of 1-3 hours before effects of THC start to appear (see **Table 5**). This may present problems when patients are trying to self-titrate their dose; they may take more (thinking that the original dose is too low) before the maximum effects are seen, which may lead to toxicity.

With regard to dosing, "low" dose is defined as less than 7 mg, medium as 7-18 mg and high as doses greater than 18 mg of THC.[9] However, tolerance to THC can develop as soon as four days after daily use, which means that higher doses may be needed to achieve the same effects.

Patterns of Use

Marijuana is the most frequently used illicit drug in the US.[10] As many as 40 percent of Americans 12 years of age or older have tried marijuana at least once, despite it being illegal in most states. However, a 2013 survey of teenagers in the 9th-12th grade that assessed patterns of usage for marijuana and other illegal drugs in the US found that despite marijuana being more accessible (due to legalization) in certain states, the trend in recent years reveals no major changes in the percentage of teenagers who have ever used, currently use, or tried marijuana prior to the age of 13.[11] (**Figure 1**).

In a relatively recent survey conducted in California, researchers interviewed about 1,700 patients who were coming to an assessment center.[12] They asked them about their marijuana use patterns and what conditions they were seeking marijuana to help alleviate. With regard to frequency of use, 67% noted that they used marijuana daily and 10% used three times a day. With regard to the time of day, 52% used it in the evening. With regard to formulation, 86% indicated the smoked route; 24% the oral route; and 22% were vaporizing cannabis. Most (79%) had failed prescription drug therapy and 48% had failed physical therapy prior to turning to marijuana.

Table 5. Pharmacokinetic Properties of THC[3]

	Smoking	Oral
Bioavailability	0.10-0.25	0.05-0.2
Peak concentrations	Within minutes	1-3 hours
Distribution t ½	30 minutes	3.8 hours
Terminal t ½	30 hours	25 hours
t½ = half-life (the time it takes for half of the drug to be eliminated from the body)		

Test Your Knowledge #1

Rank the following cannabis products from LOWEST to HIGHEST concentration of THC -- marijuana cigarettes, marijuana resin (hashish), and marijuana oil (hash oil).

Lowest Potency (5%) _____

Medium Potency (20%) _____

Highest Potency (60%) _____

Answers on page 28.

As part of this same study, the researchers also gathered billing codes for recorded reasons for approving medical marijuana patient ID cards. Pain, especially from back or neck injuries, was the most common documented reason for cannabis use. Some of the other more frequent conditions included sleep, anxiety/depression, muscle spasms, and arthritis.[12] (**Figure 2**.)

As use of cannabis for medical reasons becomes more prevalent and as more and more states enact legislation focused on medical marijuana, it becomes more important for all healthcare practitioners to increase their knowledge of the safety, efficacy, and legal issues surrounding its use.

Efficacy of Marijuana: Part One

In order to appreciate the value of the data that supports (or does not support) the use of medical marijuana, it is necessary to have an understanding of two concepts – (1) the drug approval process in the US and (2) the various types of clinical trials used in scientific research. Therefore the first part of this section will concentrate on these two topics. Part two will review the specific evidence that exists supporting the use of marijuana (synthetic and plant-based products) for various disease states.

Figure 1. Teen Illicit Drug Use Patterns[11]

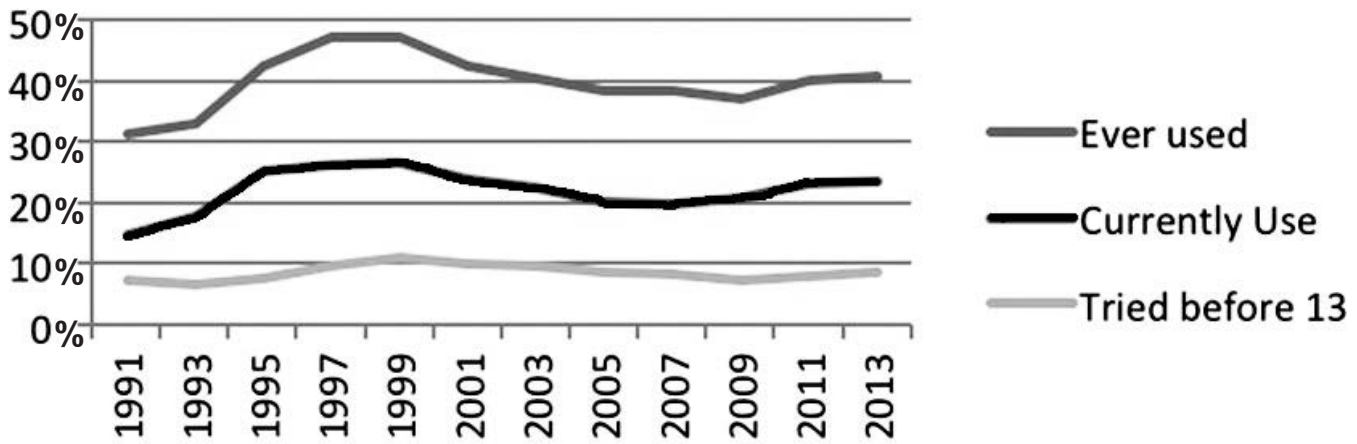
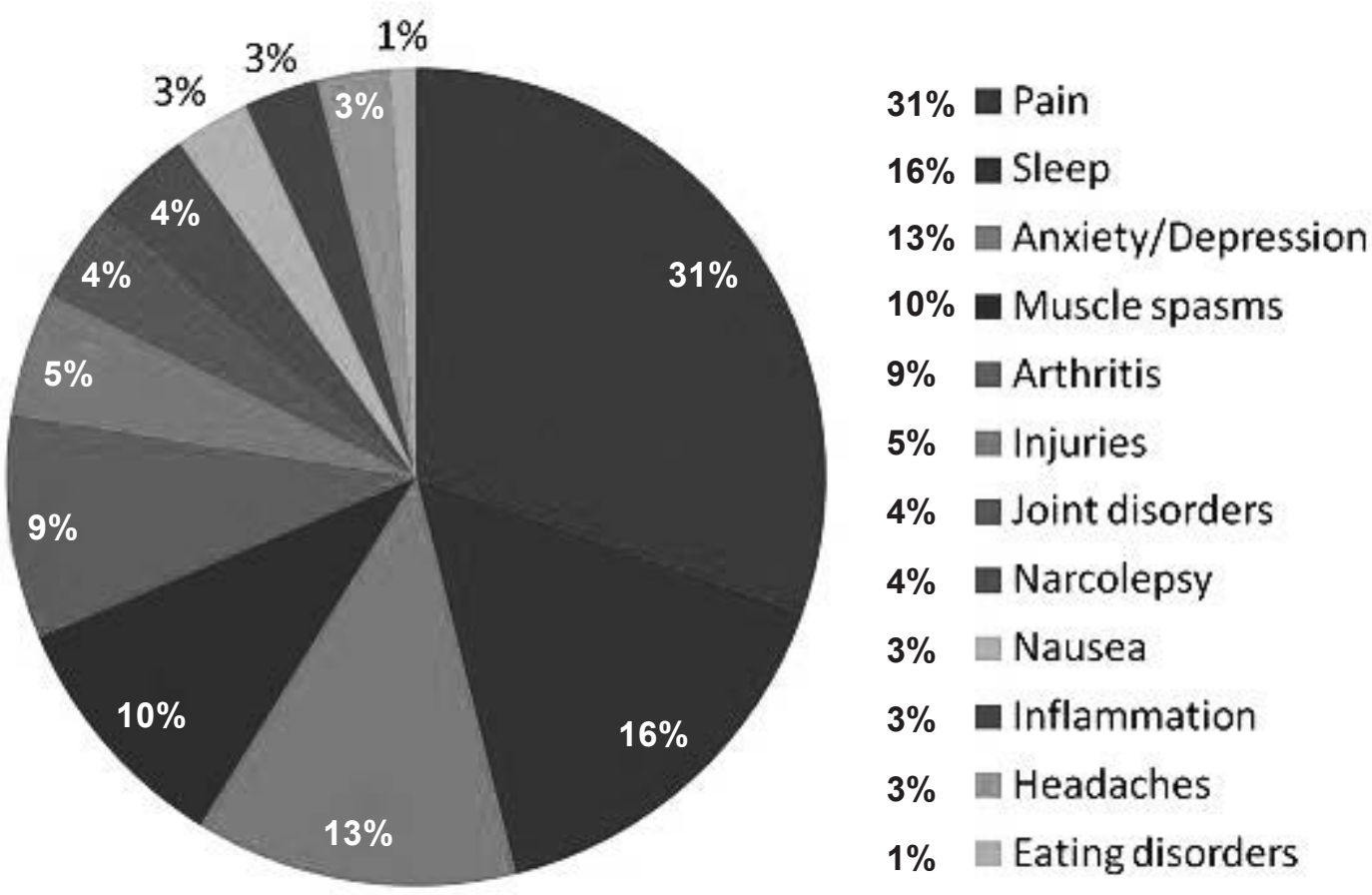
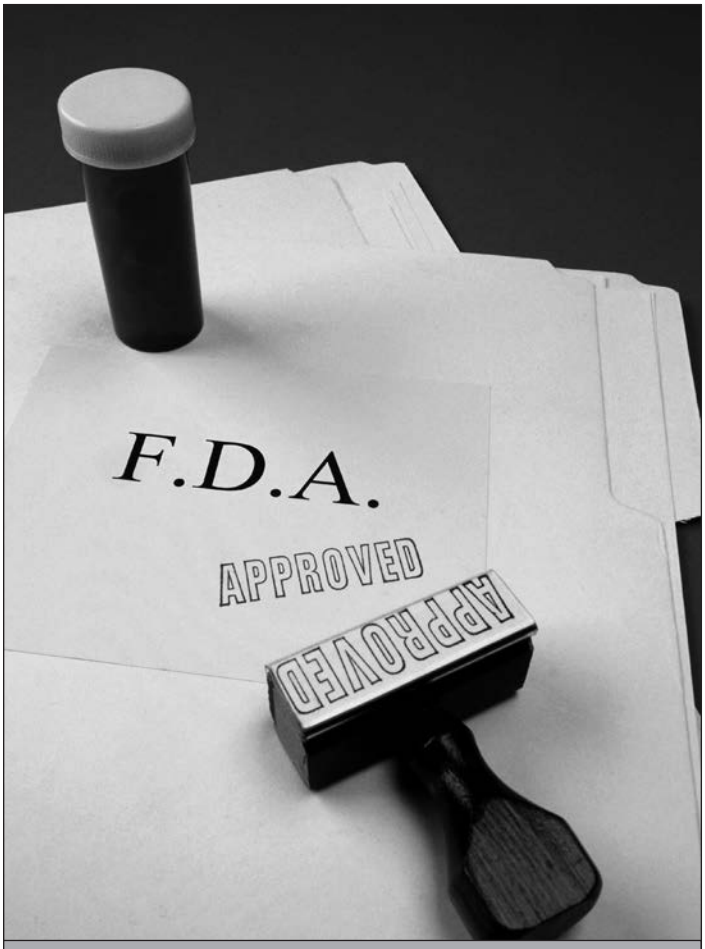


Figure 2. Patient ID Cards Issued by Physicians[12]





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Drug Approval Process

Before a drug can be marketed and approved by the Food and Drug Administration (FDA), the manufacturer of the drug has to prove that it works and is safe.[13] In order to do so, the manufacturer performs clinical trials with the drug; usually at least three types of clinical trials are needed before a drug can be approved by the FDA.[14]

Phase I studies are done using healthy volunteers. Before drugs even get to this phase, the manufacturer has to submit evidence that demonstrates that the drug has been tested and shown to be safe in animals. During phase I studies, approximately 20-80 healthy volunteers are exposed to the drug to determine how the drug is processed by the body (i.e., pharmacokinetics) and the types of side effects that the drug produces. The drug's safety profile is the main focus in phase I studies. If the phase I studies reveal no major toxicity, then the drug can move on to phase II studies.[13,14]

Phase II studies involve slightly more patients (30-300). In these studies, the focus is more on effectiveness – i.e., does the drug work? Unlike phase I studies, which used healthy volunteers, people who have the disease or condition for which the drug is targeting are the volunteers who participate in phase II studies. Usually, the patients who receive the drug are compared to a group of patients (the "control group") who do not receive the drug, but instead receive a placebo or sugar-pill designed to mimic the drug in question in every way (i.e., same shape, texture, size, smell, taste, etc.) The effectiveness of the drug being tested is evaluated by looking at certain outcomes (i.e., change in blood pressure, change in pain score, number of patients who were cured, etc.) The number and types of adverse effects reported by patients is still collected and analyzed in phase II studies. If the data from phase II studies suggest that the drug works well and is safe, then the manufacturer meets with the FDA to begin designing phase III trials.[13,14]

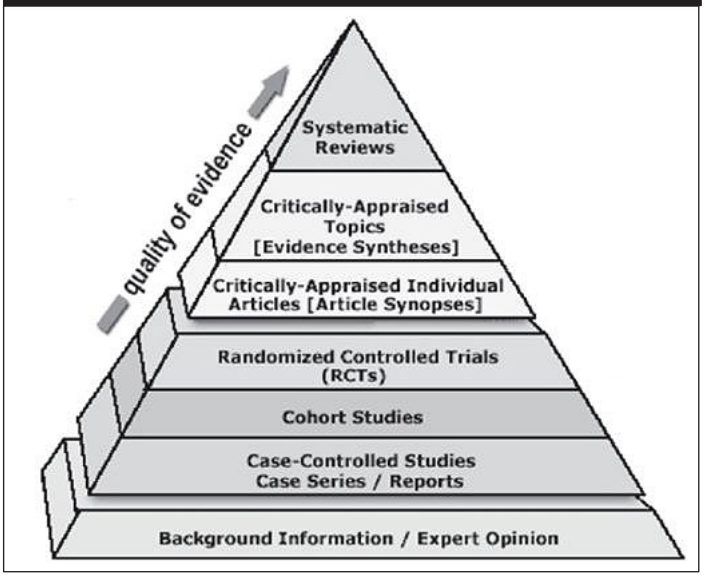
Phase III studies involve a much larger number of patients (300-3,000). In these types of studies, effectiveness and safety continue to be evaluated, but on a much larger scale. An effort is made to recruit volunteers of various backgrounds, genders, and conditions. By exposing the drug to more people, it is possible to get a better picture of how well the drug works. It also allows the researcher and the FDA to detect "rare" adverse effects.[13,14]

If the clinical trials demonstrate that the drug does, in fact, work, and that the drug is safe, then the FDA may grant the drug approval and it can be sold and marketed within the US. Some drugs are approved for general use and are sold to consumers without a prescription (over-the-counter or "OTC" drugs). Other drugs can only be dispensed with a prescription.[13,14]

Types of Clinical Trials

There are many different types of clinical trials and some have better design than others. The trials with the best design are given more "weight" when treatment decisions are made. **Figure 3** includes a pyramid of evidence[15] used by healthcare practitioners when determining which type of evidence is more credible than others. A brief overview of each of the different types of evidence is included below.

Figure 3. Pyramid of Evidence[15]



Expert Opinion

This type of evidence is at the bottom of the pyramid and should be given the least "weight" when considering different types of evidence. Although experts are knowledgeable in their area, it is possible that they could be forming their opinions on outdated or unverified information. Ideally, the medical decision to use a drug should be based on well-designed clinical studies which have thoroughly studied the safety and efficacy of a drug in humans.[13,14]

Case Control Studies

In these types of studies, the researcher is interested in determining the risk factors for a particular disease or outcome. Two groups of individuals are selected by a researcher – people who have had the outcome of interest (i.e., "cases") and people who have not had the outcome of interest (i.e., "controls"). For example, a researcher might select a group of individuals who have been diagnosed with lung cancer ("cases") and people who have not been diagnosed with lung cancer but are similar in age, weight, and health status to people who do have lung cancer ("controls"). The researcher would then interview both sets of people and ask about exposure to different risk factors. During this research project, the researcher might discover that those who have lung cancer were more likely to smoke than those who did not and therefore might come to the conclusion that smoking increases a patient's risk of getting lung cancer.[13,14]

Test Your Knowledge #2

List the two FDA approved cannabinoid (i.e., synthetic cannabis) products.

_____

_____

Answers on page 28.

Advantages of a case control study include that they are quick and efficient to perform. They are also good for detecting rare outcomes (i.e., a rare, but severe adverse effect of a medication) or for diseases that take a long time to develop. However, one of the limitations to this type of research is the potential for bias. Usually, patients are asked to think of all of the "exposures" they have had and they might not easily remember things that happened a long time ago as well as things that happened more recently.[13,14]

These types of studies are very valuable when researchers are interested in trying to find risk factors for a disease. However, if other types of studies are available that are higher on the pyramid (i.e., cohort study, randomized controlled study, systematic reviews), then the results from those types of studies should be given more "weight" than the case-control studies because they are higher on the pyramid of evidence.[13,14]

Cohort Studies

In a cohort study, the researcher selects a group of individuals who share some common characteristics such as the same age, same disease states, same medications, etc. These individuals are followed by the researcher for a period of time, during which multiple measurements or assessment are performed including laboratory tests, blood pressure measurement, monitoring for adverse effects, etc. Any decisions that are made to treat a patient are not made by the researcher, but the researcher does take note of them and analyzes their impact on the patient.[13,14]

Cohort studies can be either prospective or retrospective. A prospective study involves picking patients now and following them into the future to see what happens to them. A retrospective study involves looking back to see what happened to patients in the past. Prospective cohort

studies may allow for more control over data collection, but they are generally more expensive to perform.[13,14]

In general, cohort studies are good at identifying relationships between interventions made on patients and outcomes that occurred in those patients. However, there is the potential for error with these studies because the researcher does not have "control" over every aspect of the study. For example, the researcher does not get to decide what treatment is given to the patient, when they are monitored for safety, etc. Since these types of things can affect how patients respond, not having control over them makes it harder to conclude "beyond a shadow of a doubt" that what happened to the patient was truly due to the medication. Therefore, the results of these studies should be applied cautiously.[13,14]

Cohort studies are helpful in that they provide healthcare practitioners with some information on the potential for an agent to be used in medical practice. They are also helpful in determining the time-course of a disease or treatment. However, if higher levels of evidence are available, those types of studies should be given more "weight" when making treatment decisions for patients.[13,14]

Randomized Controlled Trial (RCT)

This type of evidence is considered the "gold standard" type of clinical trial. In an RCT, the researcher selects a group of subjects who will receive an intervention (i.e., a drug) and a group who will receive the control drug, which could be a placebo or another drug ("active control"). People who agree to participate in the study are randomized to either a control group or an intervention group. In some instances, neither the patient nor the researcher know which group the patient is randomized to – this is called a "double blind" study. Patients who are randomized to a group getting a placebo might get a pill that is of the same color, size, or shape as a patient in the intervention group to help ensure that patients and the healthcare providers cannot guess which group they have been assigned to.[13,14]

In a randomized controlled trial, the researcher has control over every aspect of the study. The researcher decides what the intervention is (i.e., what drug is being studied, what dose, etc.), how it is applied to a patient, how it will be measured and for how long. The researcher also decides what other data needs to be collected to monitor the safety and efficacy of this drug. At the end of the trial, the outcomes are measured in both groups and the results are compared and analyzed using statistics. If the treatment group performs much better than the control group, then the researcher concludes that the drug is effective and, if there are no major safety issues, then the drug can be used safely in patients who have that disease state.[13,14]

Since the researcher has control over every aspect of the study, including the intervention, what is measured, and how often, there is less room for error. This is why this type of evidence is considered to be more reliable and is therefore located closer to the top of the pyramid. One might ask why there are not more RCTs performed, since they are the best type of clinical trial. Some reasons why they are not as prevalent include the fact that, compared to other types of trials (like cohort and case-control studies), RCTs are expensive and take a longer time to perform.[13,14]

Systematic Reviews/Meta Analyses

Systematic reviews and meta-analyses are at the top of the pyramid (**Figure 3, *page 9***) because data from these types of published literature are generally considered to be the highest quality of data available on a treatment. In these types of analyses, researchers combine the results of multiple clinical trials. By combining results from multiple studies, researchers are able to feel more confident about the results that emerge.[13,14]

Although the type of clinical trial is one of the major determinants used when assessing "quality" of data, it should be noted that other characteristics are also considered when rating the quality of the data, including but not limited to: the number of patients in the trial, whether appropriate dose(s) was/were used, duration of the study, etc.[13,14]

Treatment recommendation for patients should be based on high-quality evidence. When looking for clinical trials to use when making recommendations, healthcare practitioners should consider the type of trial that was conducted as well as the "weight" of evidence of that trial. Using the pyramid of evidence helps make it clear to healthcare practitioners which trials might be more reliable than others.[13,14]

Breakout Box 1

To understand why certain types of clinical trials are valued more highly than others, think about other places where evidence is graded. Imagine that a crime has taken place. A man comes home to find that his house has been broken into and all of his valuable possessions have been stolen. He immediately calls the police, who come to the scene to investigate. During the investigation, they find one eyewitness, a neighbor ("Gordon"), who claims that he saw someone at the scene. He picks a woman out from a lineup ("Linda") and is "positive" that it was the person he saw taking things out of the house. Linda denies being there and denies stealing the man's valuables. The police also take fingerprints at the scene. The fingerprints do NOT match Linda's, but DO match another woman, "Helen", who looks very similar to Linda.

If this case were to go to trial, the eyewitness account by Gordon would be one piece of evidence used and the fingerprints would be another. A jury might give more "weight" to the fingerprints because they are more reliable (i.e., less likely to be wrong) than an eyewitness account.

Clinical trials are the evidence used when making treatment decisions and some clinical trials are more reliable (i.e., less likely to be wrong) than others. For example, a randomized, double-blinded clinical trial is considered to be the "gold standard" type of trial and is rated very highly (like the fingerprints). Other types of trials, including cohort studies, case-control studies, or case reports are considered less reliable (like the eyewitness).

Test Your Knowledge #3

Match the description of the clinical evidence (column B) to the type (column A).

Column A	Column B
_____ 1. Phase III studies	A. The lowest form of evidence
_____ 2. Expert Opinion	B. Involve 300-3,000 people; testing for efficacy
_____ 3. Case-control studies	C. The best quality of clinical evidence
_____ 4. Randomized controlled trial	D. Used to identify risk factors for a disease

Answers on page 28.

Efficacy of Marijuana: Part Two

A brief review of some of the clinical trial data that has been published is listed on the following pages, organized by medical condition. The quality of evidence that exists supporting the use of medical marijuana varies by disease state. **Figure 4 (*page 12*)** shows the quality of evidence available for each of the different formulations of marijuana. In general, there is higher quality of data available for the synthetic derivatives of marijuana (i.e., dronabinol and nabilone) and for the oral formulations. For these formulations, controlled studies represent the majority of evidence that supports their use. For the smoked formulation of cannabis, case reports and surveys (which are on the low end of the quality of evidence pyramid) make up the vast majority of clinical trials, whereas controlled studies (which are near the top of the quality of evidence pyramid), make up a smaller percentage.

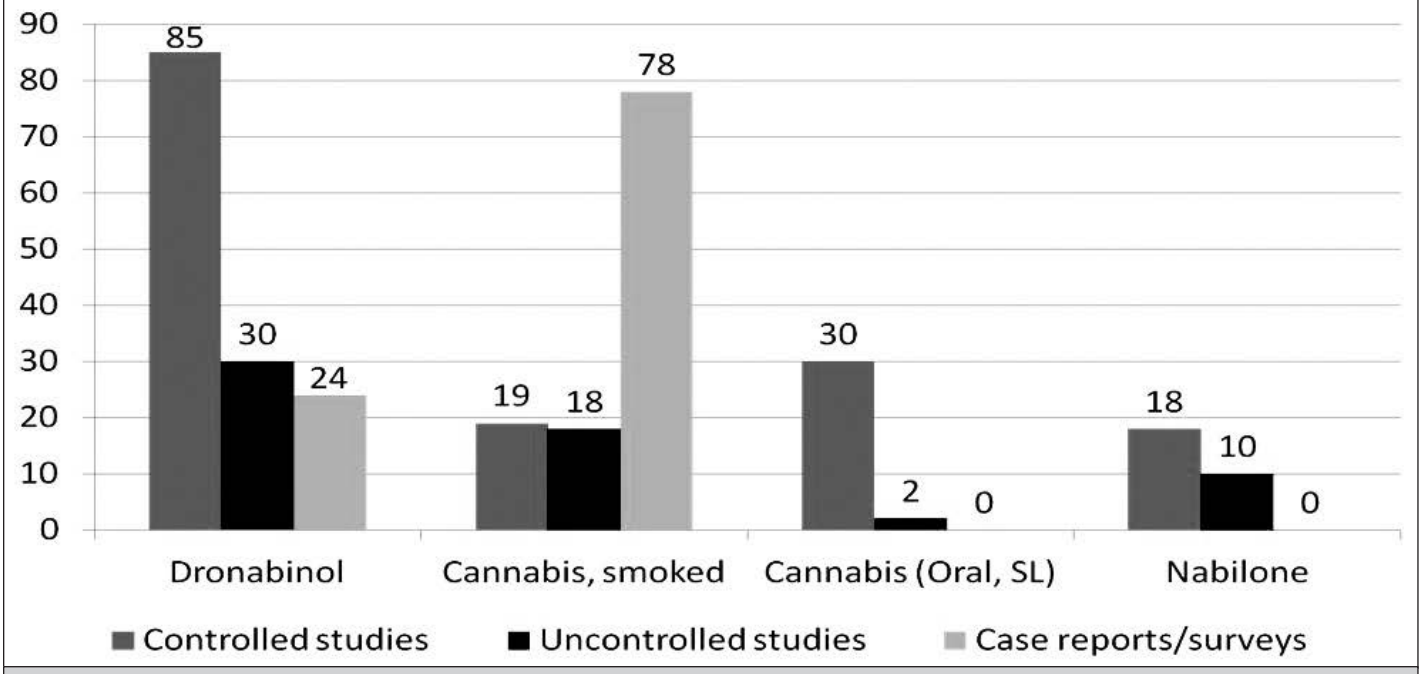
Pain

Pain is one of the disease states for which there is higher quality evidence for the use of cannabis available. In particular, it has been suggested that the use of cannabis may play a role in helping to alleviate the following types of pain: chronic pain, neuropathic (nerve) pain, fibromyalgia, rheumatoid arthritis, multiple sclerosis, and cancer pain.[3]

To date, most of the higher quality of evidence that exists is with the synthetic versions of cannabis. A recently published review summarized the results of six randomized, controlled, clinical trials that evaluated the use of various cannabinoids in the management of chronic pain.[16] The number of patients in these studies ranged from 13 to 78.[17,18,19,20,21,22] The formulation and comparator group differed in these studies: three studies compared nabilone to placebo; one study compared dronabinol to placebo; one compared nabilone to dihydrocodeine, and one compared nabiximols oromucosal spray to placebo. All of the studies demonstrated a decrease in pain compared to placebo.

There is less data involving the smoked formulation of marijuana. One published study that evaluated the smoked formulation in patients with chronic neuropathic pain found that preparations with higher concentrations of THC (9.4%) reduced pain intensity and improved quality of sleep compared to placebo.[23] Another study found benefit of the smoked formulation in HIV patients with chronic neuropathic pain with a 3.56% THC product.[24]

Figure 4. Quality of Evidence



SL = sublingual
Adapted from: http://www.cannabis-med.org/english/studies.htm (Accessed August 15, 2015)

One study that compared the synthetic cannabinoid dronabinol to smoked marijuana found that dronabinol produced results that lasted longer and was associated with lower abuse potential.[25] In a small case-series of 15 patients, 12 (80%) reported improvement in pain and mood with smoked marijuana,[26] however the effects have not yet been evaluated in more high-quality studies, so these results should be used with caution.

Marijuana for Appetite Stimulation

Marijuana may play a role in stimulating appetite in patients with late-stage cancer or HIV/AIDS. Patients with these conditions often have problems with poor appetite resulting in weight loss and there are few effective treatment options for this condition. The synthetic cannabinoid dronabinol (Marinol) is approved for the management of anorexia and cachexia in patients with human immunodeficiency virus (HIV) associated advanced immunodeficiency syndrome (AIDS).[6] HIV is a virus that attacks the immune system. Anorexia is a loss of appetite. Cachexia is a condition associated with malnutrition and physical wasting associated with certain chronic disease states.

There is evidence from two clinical trials that document that dronabinol is effective as a short-term and long-term appetite stimulant in patients with AIDS.[27,28] One study included 139 patients with AIDS-related anorexia who were randomized to receive either 2.5 mg dronabinol or placebo. In this study, patients who received dronabinol reported an increase in appetite and mood and a decrease in nausea compared to baseline. In addition, patients in the dronabinol group were able to maintain their weight whereas patients in the placebo group lost weight.[27] These effects were maintained for up to 12 months.[28]

While both of these studies suggest that dronabinol may play a role in increasing appetite in AIDS patients, it should be noted that there is no high-quality published data evaluating the use of smoked marijuana for this condition. Given the potential for variable absorption in these patients (due to their malnutrition status), it is difficult to know if the results would be the same or different with the smoked formulation.

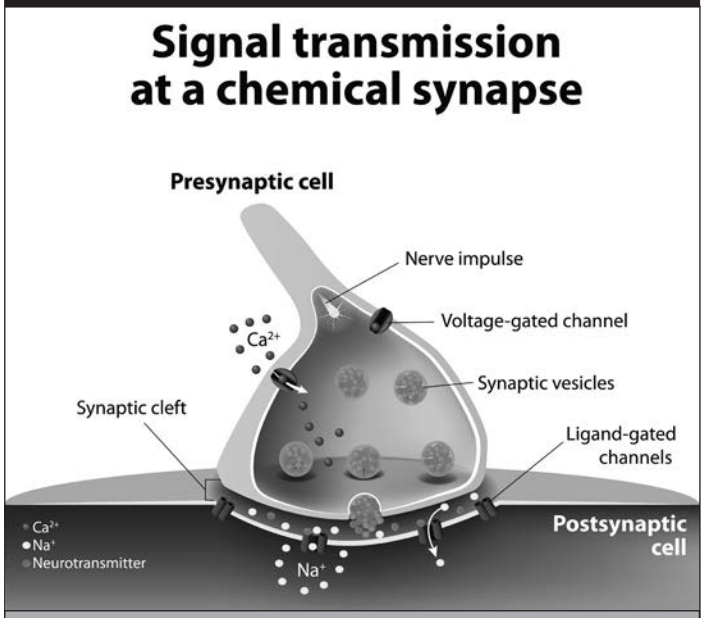
Marijuana for Multiple Sclerosis

Multiple sclerosis (MS) is a disease of the nervous system. In this condition, the myelin sheath (a protective layer surrounding the nerve fiber) is replaced with hard tissue in the brain or spinal cord, which may result in varying degrees of paralysis and/or muscle spasms/tremors.[29]

Multiple sclerosis is another condition for which there is more high-quality evidence available for the use of cannabinoids. Marijuana has been studied for its effects in controlling spasticity, muscle stiffness, pain, tremor, and incontinence (i.e., the loss of bladder control).[16] The American Academy of Neurology (AAN) guideline development subcommittee conducted a systematic review of 34 studies. Clinical indications studied include MS, epilepsy, and movement disorders. They rated the quality of the studies using a four-point classification: class I represented the highest quality of evidence and Class IV represented the lowest quality of evidence. **Table 6** shows the summary of evidence that exists for each of the MS-related symptoms.[29]

Based on their analysis of the published clinical data, the AAN developed recommendations. The highest quality of evidence is for the use of the oral cannabis extract (OCE) for the management of spasticity or central pain/painful spasms. The data supporting the other uses is not as good, but suggest that nabiximols and the smoked formulation may be effective in the management of spasticity as well. Data supporting any of the formulations evaluated does not support the use for tremor.[29,30]

Figure 5. Signal transmission at a chemical synapse



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Marijuana for Chemo-Induced Nausea & Vomiting

Nausea is defined as the immediate need to vomit. Vomiting is defined as expelling the contents of the stomach from the mouth. Patients experiencing nausea and/or vomiting may also have other symptoms including: pale skin, increased heart rate, and sweating.[31,32]

Neurotransmitters are compounds involved in spreading nervous system impulses throughout the body. Examples of neurotransmitters include: dopamine, norepinephrine, serotonin, etc. Impulses are spread when these neurotransmitters interact with receptors on the surface of nerve cells. (See **Figure 5**). When the body perceives

Table 6: Cannabis for Multiple Sclerosis (MS)[14]

Condition: AAN	Oral cannabis extract (OCE)	Nabiximols	Smoked Marijuana
Spasticity in MS	• *Effective*: subjective endpoints, objective endpoints @ 1 year • *Ineffective*: objective endpoints @ 12-15 weeks	• *Probably effective*: subjective endpoints @ 6 weeks • *Probably ineffective*: objective endpoints @ 6 weeks	• *Probably effective*: subjective endpoints, objective endpoints @ 1 year • *Probably ineffective*: objective endpoints @ 12-15 weeks
Central pain or painful spasms in MS	Effective	Probably effective	Unclear efficacy
Bladder dysfunction in MS	Probably ineffective	Probably effective	Probably ineffective
Tremor in MS	Probably ineffective	Possibly ineffective	Probably ineffective
Epilepsy	Insufficient evidence	Insufficient evidence	Insufficient evidence
AAN = American Academy of Neurology			

a toxin or a poison, nervous system impulses are sent to the vomiting center (located in the brain), which then sends out signals to various areas of the body that trigger the vomiting process. The chemotherapy receptor trigger zone (CTZ) is a specific area in the brain that is susceptible to chemically induced vomiting. Chemotherapy-induced nausea and vomiting (CINV) and pregnancy-induced nausea and vomiting usually occur as a result of the CTZ being stimulated. Some medications that are used to reduce nausea and vomiting work by blocking receptors on nerve cells that send impulses to the brain and result in vomiting.[31,32]

It is estimated that as many as 75% of all patients who receive chemotherapy experience drug-related nausea and vomiting.[33] There are many published studies that support the use of the synthetic cannabinoids (i.e., dronabinol and nabilone) for CINV. Both of these agents are approved by the FDA for use in CINV.[6,7] Although the exact mechanism of action is not known, it is thought that cannabinoids help reduce nausea and vomiting by blocking some receptors within the central nervous system (CNS) involved in vomiting. Antagonizing the peripheral CB1 receptors is also thought to be a mechanism of action (MOA), resulting in decreased intestinal motility.[34]

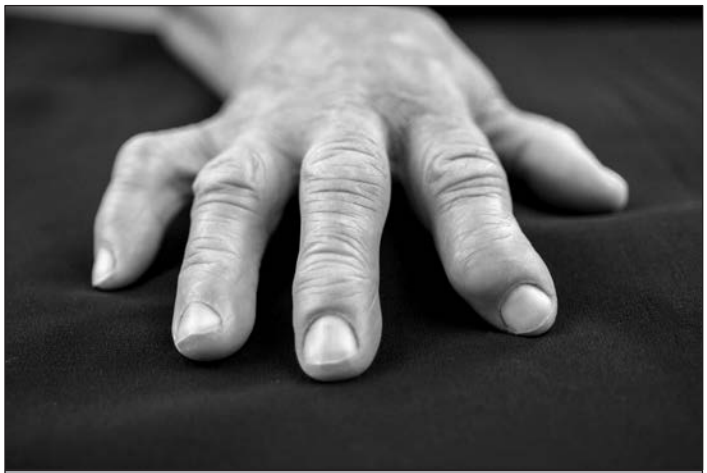
Marijuana for Epilepsy

Epilepsy is a disorder of the brain that causes patients to have multiple seizures. This is usually due to nerve cells in the brain sending out incorrect signals to the body, which may result in strange sensations, emotions, or behaviors. Some patients with epilepsy have violent muscle spasms and/or lose consciousness.[35] Many states have enacted or are considering allowing access to medical marijuana for the treatment of childhood epilepsy. This is the disease state most frequently mentioned in states that limit use to certain disease states or conditions.

Endocannabinoids or endogenous cannabinoids are substances that are produced naturally in the body that act on cannabinoid receptors (CB1 and CB2; see mechanism of action section). In epilepsy, it is thought that there may be changes in the number of CB1 receptors available at certain points in the CNS, which may cause changes in the amount of endocannabinoids present. The therapeutic effects of marijuana may be due to the CBD present in marijuana (which acts on CB1 receptors) or via the anti-anxiety or stress-relieving properties of the THC component.[36,37]

With regard to the clinical evidence available for the role of marijuana in the treatment of patients with epilepsy, there are several clinical studies done in animals that have suggested that marijuana may play a role as an anti-convulsant, but studies in animals are generally considered to be "lower" quality of evidence because we cannot be sure that humans will respond to the drug the same way; therefore, trials in humans are preferred.[38,39,40,41,42,43] Of the published data involving humans, data is limited. The highest quality of evidence comes from a case-control study that evaluated illicit drug use in patients with a first-onset seizure and those without.[44] This study suggested that use of heroin was a risk factor for seizures, whereas use of marijuana seemed to decrease the likelihood of patients getting seizures. Cocaine use had no impact.

There is some data that suggests that use of CBD was effective or partially effective in 8 patients, but this trial had a very small number of participants and was a phase I trial. A case-series of 18 patients with epilepsy suggested that patients found use of smoked marijuana helpful for seizure control. However, this data, too, should be interpreted with caution since it relied on subjective data (i.e., patients saying it worked) versus objective data (i.e., something that is measured and verifiable) and is therefore subject to bias. Of note, in both of these reports, marijuana and CBD were well tolerated.[31,32] A meta-analysis (which represents the "highest" quality of evidence) analyzed four clinical trials involving a total of 48 patients and concluded that no reliable conclusions could be drawn about the efficacy of marijuana based on the lack of high-quality evidence.[45] One case-report suggested that marijuana might play a role in causing seizures.[46] Although a case-report is low quality of evidence, this finding underlies the importance of seeking input from qualified healthcare practitioners before using the product.



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Marijuana for Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a condition that causes pain, swelling, and stiffness in the joints; usually the wrist and fingers. It is a progressive disease that may eventually lead to loss of function of the joints. (Medline Plus). Rheumatoid arthritis seems to be a condition for which medical marijuana is gaining in popularity. In the United Kingdom (UK), as early as 2005, it was listed as one of the top five indications for which people were using medical marijuana.[47] Other top five indications included: multiple sclerosis, neuropathy, chronic pain, and depression.

While there is some animal and laboratory data to suggest that cannabinoids might be effective in patients with RA, there is only one clinical study that evaluated their effectiveness for the management of this condition.[48] This study was a multi-center, double-blinded, randomized, parallel-group study that used Sativex oromucosal spray in 58 patients. In this study, the researchers found that patients in the Sativex group had less pain on movement or at rest, and better sleep quality. Similar to other studies, Sativex was well tolerated and did not have any serious adverse effects reported during the study period. While these results sound promising, noted limitations of this data include the fact that the study was only five weeks long and it used a product that is not available in the US. Larger, well-designed studies using some of the other formulations need to be performed to confirm these findings before this product is recommended consistently for patients with RA.

Marijuana for Glaucoma

Glaucoma is a condition of the eye involving increased pressure within the eyeball. Over time, this increased intraocular pressure (IOP) can result in damage to the eye and a gradual loss of vision.[49] There are published case reports from the 1970s and 1980s describing the intraocular pressure lowering effects of smoked marijuana.[50,51] Although the exact manner in which marijuana lowers IOP is unknown, it has been suggested that marijuana may affect aqueous humor production and outflow.[52] However, to date, there are no randomized clinical trials evaluating the smoked formulation. There was one published study that compared THC to CBD and placebo and found that only the THC group had a reduction in IOP.[52] This suggests that it is the THC component of marijuana and not the CBD component needed to produce this effect.

Test Your Knowledge #4

For the following disease states, circle whether the evidence supporting the use of cannabis in that disease state is high-quality or low-quality.

1.	Pain	High	Low
2.	Multiple sclerosis	High	Low
3.	Rheumatoid arthritis	High	Low
4.	Glaucoma	High	Low
5.	Parkinson's disease	High	Low

Answers on page 28.

Marijuana for Other Conditions

The role of cannabinoids has been investigated for use in the management of several conditions including: Parkinson's disease,[53,54] Crohn's disease,[55] amyotrophic lateral sclerosis,[56] asthma,[57] anxiety,[58] post-traumatic stress disorder,[59] and many others. However, to date, there are no large, well-designed clinical trials to support use in these conditions.

Table 7. Adverse Effects with Cannabis[60]

Short-term Use	Long-term or Heavy Use
• Impaired short-term memory • Impaired motor coordination • Altered judgment • Paranoia/psychosis	• Addiction • Altered brain development • Effects on education • Cognitive impairment (mental function) • Decreased life satisfaction • Chronic bronchitis (inflammation of the lungs) • Risk of chronic psychosis

Safety Concerns with Marijuana

Table 7 depicts some of the adverse effects associated with both short and long-term use of marijuana. In marijuana-naïve patients, acute ingestion of marijuana (via smoking) frequently causes the following effects: increased heart rate, dry mouth, nausea/vomiting, red eyes, changes in blood pressure, euphoria, anxiety, impaired motor coordination, and impaired memory or thinking ability.[60] In chronic users, additional effects may be seen depending on how much is used and whether the use is short-term or long term. The lethal dose of marijuana is between 15-70 grams.[60] An overview of other potentially serious complications from marijuana use is discussed later in this module.

Table 8. Concentration of THC in the Blood and Odds of Being at Fault in a Motor Vehicle Accident[91]

THC Conc (ng/mL)	Unadjusted OR	95% CI
<1	2.18	1.22-3.89
1-2	2.54	1.86-3.48
3-4	3.78	2.24-6.37
≥5	4.72	3.04-7.33

< = less than
≥ = greater or equal to
CI = confidence interval
OR = odds ratio
THC = tetrahydrocannabinol

Adverse Effects

Driving

Marijuana is associated with dose-related impairment in cognitive (mental judgement) and psychomotor (physical) skills. Cannabis intoxication can impair many skills necessary for driving including: reaction time, perception, short-term memory, attention span, motor skills, tracking, and skilled activities.[61] Two published analyses have evaluated the affect of marijuana use on motor vehicle collisions (MVC). In both of these studies, there was an increased risk of MVC associated with marijuana use. One analysis showed that marijuana use almost doubled the risk of MVC.[62] Another suggested that marijuana use almost tripled the risk for MVC.[63]

A separate analysis looked at the likelihood that the impaired driver was at fault for the collision. Researchers found that as the THC level increased, the likelihood of the impaired driver being at fault increased dramatically. The impaired driver was more than three times more likely to be at fault in MVCs compared to non-marijuana users. In addition, the odds of the impaired driver being at fault increased as the concentration of THC increased, suggesting that the more marijuana that is present in a driver's system, the more likely they are to be at fault for a MVC. (**Table 8**).[91]

In Australia, it is illegal to drive with a blood THC greater than 0. In Colorado, lawmakers are considering enacting a legal limit of 5 ng/ml THC level or less. One of the logistical issues that some people are struggling with is how to detect blood levels – since there is no "point of care" device, the driver has to be taken back to the station and it may be 3-4 hours later before a level is drawn and at that time it would be much lower and may not adequately represent the amount of impairment at the time of the crash. In addition, studies have shown that blood levels of cannabis do not correlate as well with intoxication as alcohol levels do.[64]

Lung Complications

There are many lung concerns with the use of marijuana; especially when it is inhaled. Marijuana smoke has some of the same chemicals as tobacco smoke,[65] including benzopyrene, a chemical found in tobacco smoke that has been associated with an increase in lung cancer.[66] However, unlike tobacco cigarettes, marijuana is typically smoked without a filter. In addition, marijuana use typically involves a much deeper inhalational technique, and smokers usually hold their breath for a longer period of time, compared to cigarette smoking. Finally, while the size of tobacco cigarettes is fairly standardized, the size of smoked marijuana products can be variable. All of these factors increase the likelihood of higher exposure to toxic substances. There is some in vitro data (in test tube) that suggests that THC may cause malignant (cancer-forming) cell growth or tumor growth.[67] Of note, due to the potential of environmental exposure to toxic chemicals, many marijuana users have started using a vaporized route of administration. This route allows for inhaled delivery of cannabis to the lungs with less harm to the environment.

The risk for lung cancer associated with marijuana smoking has also been evaluated in a large meta-analysis that involved 19 studies.[68] Results of this analysis suggested that when marijuana is smoked, there is an increase in tar exposure compared to tobacco smoking. There was also an increase in bronchial cell abnormalities in the lungs compared to non-smokers; although this appeared to be more pronounced when marijuana users were also tobacco smokers.[68] Although this evaluation did not find an association between marijuana use and lung cancer, it was noted that the age of the participants in the trials evaluated were young and the studies may not have been long enough to detect lung cancer.

In addition to lung cancer, smoking marijuana may also be associated with other respiratory complications. A recently published meta-analysis analyzed data from 34 studies to determine the short-term effects of marijuana smoking on airway response and the long-term effects of marijuana smoking on pulmonary function and respiratory complications.[65] Nine of the twelve studies that evaluated the effects of marijuana smoking on airway response found an increase in bronchodilation associated with short-term use. With regard to the effects of long-term marijuana smoking on pulmonary function and respiratory complications, the results from 14 published studies were evaluated. There was no consistent association between marijuana smoking and pulmonary function (as assessed by FEV1/FVC ratio, DLco, or airway hyperreactivity). All found that respiratory complications were associated with long-term use including the following symptoms: an increase in cough, sputum (phlegm) production, wheezing, bronchitis, dyspnea (shortness of breath), pharyngitis, worsening of asthma/cystic fibrosis, hoarse voice, and abnormal chest sounds.[65]

Dependence

As many as 9% of people who use marijuana will become addicted.[69] This increases to 16% for those who began using marijuana during adolescence and increases to as high as 50% of those who use marijuana on a daily basis.[60] A cannabis withdrawal syndrome has been identified[70] which may make it difficult for users to stop. Symptoms include: irritability, sleeping problems, anxiety, cravings, and poor mood. Use of marijuana during adolescence is particularly troubling because data suggests that this population is 2-4 times more likely to become dependent within the first two years of use.[71]

There is some data that suggest that use of marijuana may increase the likelihood of use of other illicit drugs later on in life such as heroin, cocaine, or methamphetamine. It is sometimes called a "gateway" drug for this reason. The Christchurch Health and Development Study (CHDS) followed a cohort of children in New Zealand from birth to age 25.[72] An annual assessment of drug use revealed that increased frequency of cannabis use was associated with use of other illicit drugs as well as illicit drug abuse or dependence.[73] In addition, the earlier the age that a person started using marijuana, the more likely they were to use other illicit drugs. Frequency of use also seemed to impact the extent of other illicit drug use. One study found that adolescents and young adults who used cannabis weekly were 2-3 times more likely to use other illicit drugs and those who used it daily were 6 times more likely to use cigarettes.[74]

Social Impact

The Ferguson study also evaluated the association between cannabis use by age 21 and its effects on the following outcomes: education/income, welfare dependence/unemployment, and relationship and life satisfaction. Use of cannabis prior to the age of 21 was associated with lower likelihood of obtaining a degree, less income, increased likelihood of welfare dependence, increased unemployment, and decreased relationship and life satisfaction. For most outcomes evaluated, there was a dose-related effect, meaning that the more marijuana that was used, the worse the outcomes tended to be.[73]

Brain Development

The brain remains in a constant state of development from birth until at least age 21.[75] During these periods, the brain is more susceptible to adverse effects from environmental toxins and other substances affecting the brain, including THC. Studies have suggested that use of marijuana during adolescence may impair connections in the brain associated with alertness, self-conscious awareness, learning, and memory.[76] Another study has shown a relationship between persistent marijuana use and lower IQs. These effects were not fully reversible when cannabis use was stopped.[77]

Psychological Reactions

Use of cannabis has been associated with depression and anxiety.[58,78] It has also been suggested that marijuana use prior to the age of 15 may increase the likelihood of experiencing symptoms of schizophrenia as an adult.[79,80] Use may also precipitate psychoses in patients with schizophrenia. However, high-quality data to support these hypotheses is limited at the current time.

Other Adverse Effects

Although there is some data to suggest that use of cannabis may be linked to erectile dysfunction in men, data is conflicting and there is a lack of high-quality evidence.[81]

Drug-Drug Interactions

Marijuana has the potential to interact with many medications. **Table 9** includes a list of all of the medications that have been reported to interact with marijuana. In some instances, use of marijuana with certain prescription medications can lead to increased or decreased levels of the medication. Marijuana has also been shown to interfere with platelet aggregation, which may lead to a higher risk of bleeding if it is used with other medications known to increase the risk of bleeding (such as anticoagulants, antiplatelet agents, and certain pain medications). Due to THC's effects on increasing heart rate, it should be used cautiously in patients with cardiac disease and in patients taking other medications that can also increase heart rate.[82] In addition, combined use with tobacco may lead to additional increases in heart rate and carbon monoxide levels.

Test Your Knowledge #5

List three adverse effects associated with marijuana use.

_____

_____

_____

Answers on page 28.

Drug-Disease Interactions

Based on its mechanism of action and adverse effect profile, use of marijuana should be used with caution in patients with the following conditions: immunocompromised states, psychiatric illness, cardiac disease, respiratory disease, vertigo, pregnancy, and obesity. Immunocompromised individuals may include patients with HIV, lupus, rheumatoid arthritis, or patients who have had an organ transplant. Use in these patients may cause undesirable additive immunosuppression.[83] In addition, there is data that suggests that marijuana may worsen certain psychiatric disorders including depression, and may also cause hallucinations, and/or violent behavior in patients with schizophrenia.[80]

Legal/Regulatory Issues

The Food and Drug Administration (FDA) regulates all drug products marketed in the US. To date, the FDA has not approved any plant-based (botanical) marijuana products. However, the FDA has approved two synthetic products: dronabinol (Marinol), a synthetic THC product, and nabilone (Cesamet), a synthetic product with a chemical structure that is similar to THC. Marinol is approved for the treatment of anorexia associated with weight loss in patients with acquired immune deficiency syndrome (AIDS).[6] It is also approved as a last-line agent for the management of nausea and vomiting associated with chemotherapy (CINV) in patients with cancer,[6] which means that the patient must have tried other agents approved for CINV and found no relief with them before Marinol can be prescribed for CINV. Dronabinol is classified federally as a schedule III substance. Cesamet is also approved as a last-line agent for the management of nausea and vomiting associated with CINV.[7] Nabilone is classified federally as a schedule II substance. Nabiximols (Sativex) is another liquid formulation derived from two strains of *Cannabis sativa*. Although not approved in the US, it is available in Canada as an oromucosal spray under the brand name of Sativex.[8]

Table 9. Drugs that May Interact with Marijuana[92]

Drug Class	Drugs	Effects	Severity
Alcohol Deterrent	disulfiram (Antabuse)	Hypomania	Moderate
Anesthetics	enflurane (Ethane), halothane (Fluothane), isoflurane (Forane), methoxyflurane (Penthrane)	May decrease the levels of these drugs	Moderate
Antibiotics	clarithromycin (Biaxin), erythromycin	Increased levels of these drugs	Moderate
Anticoagulants	aspirin, clopidogrel (Plavix), diclofenac (Voltaren), ibuprofen (Advil), naproxen (Naprosyn, Anaprox), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, warfarin (Coumadin)	Might increase the risk of bleeding by interfering with platelet aggregation	High
Antidepressants	fluoxetine (Prozac)	Hypomania	High
Barbiturates	pentobarbital (Nembutal), phenobarbital (Luminal), secobarbital (Seconal)	May increase the drug levels of the barbiturate	High
Calcium channel blockers	diltiazem (Cardizem), verapamil (Verelan)	Increased levels of these drugs	Moderate
Central Nervous System (CNS) Depressants	triazolam (Halcion)	Use of these agents with marijuana may increase CNS depression	High
Contraceptives	estrogens	May interfere with the effects of estrogen.	Moderate
HIV medications	indinavir (Crixivan), nelfinavir (Viracept), saquinavir (Invirase)	Increased levels of these drugs	Moderate
Immunosuppresants	cyclosporine (Neoral)	Increased levels of these drugs	Moderate
Lipid Lowering Agents	lovastatin (Mevacor)	Increased levels of these drugs	Moderate
Other	ethanol, acetaminophen (Tylenol), theophylline, chlorzoxazone (Parafon Forte)	May decrease the levels of these drugs	Moderate

Breakout Box 2: Controlled Substances Schedules[84]

Schedule I

To be classified as a schedule I, a drug or substance must meet the following criteria: (1) the drug/substance has a high potential for abuse, (2) the drug/substance has no acceptable use in medical treatment, and (3) the drug/substance is unsafe when used under medical supervision. Examples of schedule I substances include (according to federal law): heroin, lysergic acid diethylamide (LSD), and 3,4-methylenedioxymethamphetamine (i.e., "Ecstasy").

Schedule II

Substances classified as a schedule II have a high potential for abuse that may lead to severe physical or psychological dependence. Examples of substances in schedule II include some narcotics (i.e., hydromorphone, fentanyl, methadone, meperidine, codeine, e.g.,) and some stimulants used for the treatment of attention-deficit hyperactivity disorder (ADHD) such as mehylphenidate (Ritalin) and amphetamine (Dexedrine, Adderall).

Schedule III

Substances classified as a schedule III substance have a potential for abuse that is less than that of substances in schedules I and II. However, use of these agents may still lead to low-moderate levels of physical dependence or a high level of psychological dependence. Examples of substances in schedule III include certain codeine-containing products (i.e. Tylenol with Codeine), buprenorphine/naloxone (Suboxone), ketamine, and anabolic steroids (Depo-Testosterone).

Schedule IV

Substances classified as a schedule IV substance have a low potential for abuse compared to agents in schedules III. Examples of schedule IV substances include certain anti-anxiety medications such as alprazolam (Xanax), clonazepam (Klonopin), and diazepam (Valium), for example as well as carisoprodol (Soma).

Schedule V

Substances classified as a schedule V substance have a low potential for abuse compared to agents in schedules IV and mostly consist of preparations that contain a small amount of certain narcotics. Examples of schedule V substances include Phenergan with Codeine and Robitussin with Codeine.

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Regulatory Status of Marijuana

Breakout Box 2 includes definitions of the controlled substance schedules. Substances may be chemicals or medications. When deciding how to classify a substance, the following information is considered: (1) whether there is a current medically accepted use for the product in the US, (2) the abuse potential and (3) the likelihood of the substance causing dependence.[84]

Marijuana is classified as a schedule I substance by the federal government. As a schedule I substance, marijuana is illegal for any person to manufacture, dispense, distribute, or possess according to federal law. However, several states have enacted legislation (**Table 10**) to allow for the use of marijuana medically. A few other states have enacted legislation that decriminalizes the use of marijuana for recreational purposes.[85]

In 2009, the Department of Justice (DOJ) noted that it would not use federal resources to prosecute individuals who were distributing marijuana to seriously ill patients for medical purposes in states with medical marijuana laws.[86] More recently, in 2013, the DOJ updated their enforcement policy and noted that they will "…defer the right to challenge the legalization laws at this time" in states such as Colorado and Washington, that allow for the possession of small amounts of marijuana, although they also noted that they expect states to develop strong

Table 10. States with Medical Marijuana/Cannabis Programs[85]

State	Specific Conditions?
Alaska	Yes
Arizona	Yes
California	No
Colorado	Yes
Connecticut	Yes
Delaware	Yes
District of Columbia	Yes
Guam	Yes
Hawaii	Yes
Illinois	Yes
Maine	Yes
Maryland	Yes
Massachusetts	Yes
Michigan	Yes
Minnesota	Yes
Montana	Yes
Nevada	Yes
New Hampshire	Yes
New Jersey	Yes
New Mexico	Yes
New York	Yes
Oregon	Yes
Rhode Island	Yes
Vermont	Yes
Washington	Yes

enforcement efforts that focus on the top marijuana-related priorities of the DOJ administration including the prevention of: (1) distribution to minors (2) revenue from going to organized gangs/cartels, (3) diversion to states where marijuana is not legal, (4) using marijuana as a cover-up for trafficking of other illegal drugs or activity, (5) violence or the use of firearms with the distribution of marijuana, (6) drugged driving associated with marijuana use, (7) growing of marijuana on public lands, and (8) possession of marijuana on federal property.[87,88]

As of August 2015, there are 23 states, the District of Columbia, and Guam that have a state medical marijuana/cannabis program (See **Table 10**). An additional 17 states have laws passed by the state legislature that allow for limited access to marijuana by specifying that only certain formulations of marijuana can be used. (**Table 11**).

Table 11. States with Limited Access Marijuana-Product Laws[85]

State	Specific Conditions?
Alabama	Debilitating epilepsy or life-threatening seizures
Florida	Cancer, medical condition, or seizure disorders with symptoms alleviated by low-concentration THC products
Georgia	End-stage cancer, ALS, MS, seizure disorders, Crohn's disease, mitochondrial diseases, Parkinson's disease, Sickle Cell disease
Iowa	Intractable epilepsy
Kentucky	Intractable seizure disorders
Louisiana	Yes
Mississippi	Debilitating epileptic condition or related illness
Missouri	Intractable epilepsy unresponsive to three or more treatments
North Carolina	Intractable epilepsy
Oklahoma	People under the age of 18 with Lennox-Gastaut Syndrome, Dravet Syndrome, or other severe epilepsy not adequately treated with approved drugs
South Carolina	Lennox-Gastaut Syndrome, Dravet Syndrome, or other severe epilepsy not adequately treated with approved drugs
Tennessee	Intractable epilepsy
Texas	Intractable epilepsy
Utah	Intractable epilepsy that has not responded to three or more treatment options suggested by a neurologist
Virginia	Intractable epilepsy
Wisconsin	Seizure disorders
Wyoming	Intractable epilepsy or seizure disorders

ALS: Amyotrophic Lateral Sclerosis
MS: Multiple Sclerosis

For example, the state of Florida requires that only cannabis with low THC concentrations (defined as less than 0.8%) and high CBD (defined as greater than 10% by weight) may be sold.[85] Whereas other states, like Alabama and Kentucky only allow the use for research pur-

poses.[85] One state, Idaho, had legislation approved that was vetoed by the Governor.[85]

There are many differences among the states with regard to how the programs are developed. For example, some states differ in how they are classifying marijuana. As of 2013, Connecticut has reclassified marijuana as a schedule II agent.[89] Most states have allowed for the creation of marijuana dispensaries as the primary means for dispensing the product.

Logistics

There are many logistical factors that state legislatures must consider when operationalizing the use of medical marijuana. Issues to consider include the following:

- *What will be dispensed*: Many of the states that allow for limited use of medical marijuana have specific definitions in place regarding which substance can be dispensed (i.e., Kentucky only allows for the use of cannabidiol). Others specify maximum percentages of active ingredients in the formulation (i.e., less than 0.8% THC and greater than 10% CBD in Florida).[85]
- *Who will dispense*: Some states (i.e. Connecticut) require the use of pharmacists and pharmacy technicians to dispense the product provided that they meet certain criteria. For example, Connecticut allows pharmacists in good standing with an active license to open a dispensary facility and they allow pharmacy technicians over the age of 18 who are affiliated with a state-licensed dispensary and have been registered for the past five years to assist in the dispensing of medical marijuana.[90]
- *Who it will be dispensed to*: Of the 25 states/areas with medical marijuana/cannabis programs in place, all but one (California) allow the use of medical marijuana for certain medical conditions. Of the 17 states that allow for limited use of medical marijuana, 100% outline specific medical conditions for use.[85]
- *Where it will be dispensed*: Of the 25 states/areas with medical marijuana/cannabis programs in place, most (72%) allow dispensaries.[85]
- *How appropriate patients will be identified*: Of the 25 states/areas with medical marijuana/cannabis programs in place, all but one (Washington) have a system in place that utilizes a patient registry or ID card to ensure that only legitimate patients receive access to medical marijuana.[85]

Research

Even though marijuana is classified federally as a schedule I substance, the federal government has a provision in place to allow for its use in medical research. Certain states with limited access laws also address this issue (**Table 11, *page 21***). Patients enrolled in US clinical trials using medical marijuana usually are provided with a cannabis strain or blend that is grown at a farm at the University of Mississippi.[87]

Recreational Use

Two states currently allow the use of marijuana for recreational use – Colorado and Washington. A few other states, including Alaska, the District of Columbia, and Oregon have received state approval, but have not yet operationalized the process yet.

Summary

Marijuana may have a role in some disease states, although the quantity and quality of evidence varies by formulation and disease state. Larger and better-designed studies are needed to determine its potential in other disease states. Even though marijuana is a naturally occurring substance, the drug is not without risk. There are a number of different safety issues to consider. Marijuana's adverse effect profile may limit use for some patients. In addition, unlike other approved drugs, the dosing is not exact in many dosage forms and it is difficult to predict response in patients.

Regulatory and clinical information on medical marijuana is constantly changing. Laws and processes differ from state to state. Pharmacists, pharmacy technicians, and other healthcare professionals need to stay up to date on legal issues surrounding the use of medical marijuana in their state.

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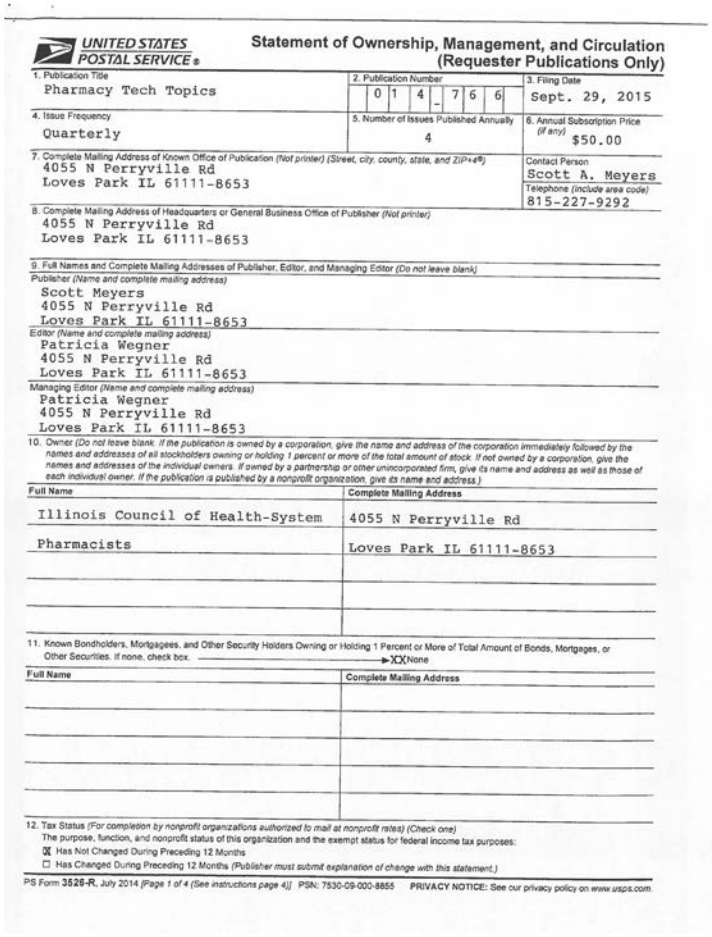

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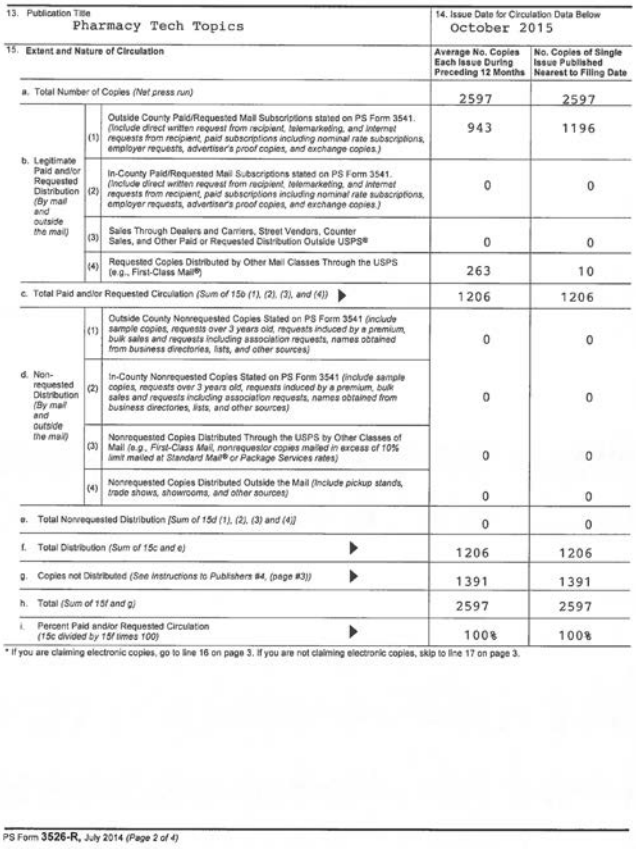

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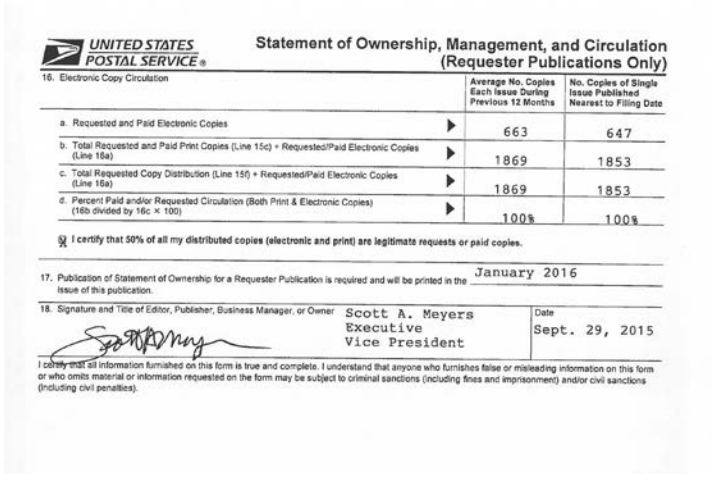

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17. Publication of Statement of Ownership for a Requester Publication is required and will be printed in the January 2016 issue of this publication.

18. Signature and Title of Editor, Publisher, Business Manager, or Owner: Scott A. Meyers, Executive Vice President — Date: Sept. 29, 2015

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

ANSWER KEY: TEST YOUR KNOWLEDGE EXERCISES

Exercise #1:
Lowest potency (5%) cigarettes
Medium potency (20%) resin
Highest potency (60%) oil

Exercise #2:
dronabinol (Marinol)
nabilone (Cesamet)

Exercise #3:
1. B
2. A
3. D
4. C

Exercise #4:
1. High
2. High
3. Low
4. Low
5. Low

Exercise #5:
Any of the below adverse effects:
- impaired driving
- lung cancer
- breathing complications
- addiction
- altered brain development
- erectile dysfunction

SELF ASSESSMENT QUESTIONS

1. **Which of the following is the major psychoactive component of cannabis?**
   A. Cannabidiol
   B. Delta-9-tetrahydrocannabinol (THC)
   C. Dronabinol
   D. Nabilone

2. **Which of the following synthetic versions of marijuana is approved in the United States?**
   A. Dronabinol (Marinol)
   B. Nabilone (Cesamet)
   C. Nabiximols (Sativex)
   D. A and B

3. **Dronabinol (Marinol) and nabilone (Cesamet) are approved by the Food and Drug Administration (FDA) for use in which condition?**
   A. Rheumatoid arthritis
   B. Crohn's disease
   C. Chemotherapy-induced nausea and vomiting
   D. Pain

4. **Which of the following is true about marijuana:**
   A. Once consumed, it is eliminated from the body quickly
   B. Tolerance does not develop with frequent marijuana use
   C. Marijuana tends to stay in fat cells
   D. Ingesting marijuana orally leads to a quicker onset of effects

5. **Of the following choices, which type of evidence is considered the "gold standard" and has the highest weight when considering evidence?**
   A. Randomized controlled trial
   B. Cohort study
   C. Case control study
   D. Case report

6. **On the pyramid of evidence, which of the following types of published literature ranks the highest?**
   A. Case-control study
   B. Randomized, controlled trial
   C. Systematic review (meta-analysis)
   D. Cohort study

7. **Which of the following indications have the BEST quality of evidence supporting the use of medical marijuana?**
   A. Rheumatoid arthritis
   B. Epilepsy
   C. Inflammatory bowel disease (i.e., Crohn's or Ulcerative Colitis)
   D. Pain

8. **Which of the following is/are common side effects seen soon after marijuana ingestion?**
   A. Increased heart rate
   B. Decreased heart rate
   C. Improved thinking ability
   D. Increased salivation (i.e., drooling)

9. **Using cannabis while driving can affect:**
   A. Attention span
   B. Reaction time
   C. Motor skills
   D. All of the above

10. **In which country is it illegal to drive if there is any marijuana in the system?**
    A. The United States
    B. Mexico
    C. Australia
    D. Canada

11. **Which of the following is NOT a safety concern with the use of medical marijuana?**
    A. Impaired driving
    B. Impaired sexual health
    C. Psychosis
    D. All of the above are safety concerns

12. **The risk for addiction to marijuana is highest in which patient population?**
    A. Adults (greater than 18 years old)
    B. Adolescents (13-18 years old)
    C. Geriatric patients (greater than 65 years of age)
    D. Males

13. All of following statements are true regarding marijuana use and addiction EXCEPT:
A. Teenagers are the most likely to become addicted to cannabis
B. Long-term, consistent use may lead to withdrawal symptoms
C. Use of cannabis may lead to use of other illicit drugs
D. Addiction is more likely if a person starts using as an adult

14. Linda is a 57 year old nurse with high blood pressure, high cholesterol. She was recently diagnosed with rheumatoid arthritis (RA). She is currently taking lovastatin for her high cholesterol and verapamil for her hypertension. She would like to try using marijuana for her RA. Which of the following statements provides the best treatment recommendation and supporting rationale?
A. Yes, she should use marijuana because there is high-quality evidence to support its use in patients with RA.
B. Yes, she should use marijuana because it is safer than prescription drugs.
C. No, she should NOT use marijuana because there are drug interactions with her current medications.
D. Yes, she should use medical marijuana because it will also help lower her cholesterol.

15. A substance or drug that is deemed to have no medical use and a high potential for abuse is classified as which schedule?
A. Schedule I
B. Schedule II
C. Schedule III
D. Schedule IV

16. According to federal law, medical marijuana is classified as which schedule?
A. Schedule I
B. Schedule II
C. Schedule III
D. Schedule IV

17. In which of the following states is the use of marijuana for recreational purposes legal?
A. Florida
B. Alaska
C. Utah
D. Washington

18. In some states, it is required that _____ dispense medical marijuana.
A. nurses
B. doctors
C. dietitians
D. pharmacists

19. When it comes to marijuana enforcement, all of the following are considered top priorities of the Department of Justice EXCEPT:
A. Distribution to minors
B. Growing marijuana on public lands
C. Diversion to states where marijuana is not legal
D. Possession of marijuana for a legitimate medical need

20. Ed is a 61 year old pharmacist who works in a chemotherapy center in Utah. A patient asks him if he knows anything about medical marijuana. In particular, the patient wants to try using it for his seizures, but he wants to know if he can do this? How should Ed respond?
A. No, it is illegal to use medical marijuana in Utah for any condition.
B. Yes, he may be able to use it, but only for chemotherapy-induced nausea and vomiting (CINV).
C. No, he cannot use it because it is only approved for children.
D. Yes, he may be able to use it, but only after he has failed 3 other treatment options.